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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Finnegan Henderson Farabow
Garrett & Dunner
1300 I Street NW
Washington, DC 20005

EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/555,139	Applicant(s) VAN SCHARRENBURG ET AL.	
	Examin r Jennifer E. Graser	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/14/03, Paper No. 20D, has been entered.

Claims 10-28 are currently pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-26 are vague and indefinite because it is unclear what is encompassed by the term "particulate immunogen". The Webster's II New Riverside University Dictionary defines the word 'particulate' as "Of, relating to, or made up of separate particles". It is unclear what is included in this definition, i.e., peptides, conjugates, whole cell attenuated vaccines, etc.. Clarification is requested. The specification at page 4, lines 19-23, state that "particulate" means

any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms". The term 'association' is generally accepted to mean any 'relationship'. It is unclear how these antigens are to be associated. Does this encompass membrane bound antigens on the surface of a whole cell vaccine? Clarification is requested.

Response to Applicants' Arguments:

Applicants have argued that while the former definition ("particulate" defined as any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms) is included in the specification, the specification also contains a preferable embodiment which comprises "aggregates, clusters, virosomes, rosettes, virus-like immunogen particles and the like". This has been fully and carefully considered but is not deemed persuasive to overcome the rejection. Applicants provide a fairly broad introductory definition followed by a more narrow definition as a preferred embodiment. In order to invoke the narrower definition specific verbiage must be included in the claim. The examiner must select the broadest definition of the term "particulate immunogen" when interpreting the claim. If Applicants wish to claim the preferred embodiment then the claim should be amended to limit to such embodiment.

Claims 10, 16, 18, 19 and 20 are vague and indefinite due to the phrase "characteristic of *E.coli*". It is unclear whether this statement is intended to imply that the heat-labile enterotoxin is the one from *E.coli* or something else. It is suggested that the claims be amended in order to delete the word "characteristic" in order to eliminate ambiguity, i.e., heat-labile enterotoxin of *E.coli*. Alternatively, Applicants may amend the claims to recite "heat-labile *E.coli* enterotoxin.

This will include the scope of the claim that Applicant desires, i.e., recombinant as well as naturally obtained, and will clear up the ambiguity associated with the phrase 'characteristic of'. With respect to "characteristic of a microorganism", whether or not a non-pathogenic microorganism is used to express an immunogen from a pathogenic microorganism, said immunogen is still from a pathogenic microorganism.

Claim 13 is vague and indefinite due to the term "derived". The term "derived" does not provide the character or properties from the source that are to be retained in the final product, e.g., paper is derived from wood but is very different from wood. The term "derived" should be deleted from the claim. Whether or not a non-pathogenic microorganism is used to express an immunogen from a pathogenic microorganism, said immunogen is still from a pathogenic microorganism. If non-pathogenic E.coli is transformed with DNA encoding antigen from *N.menigitidis,* the expressed immunogen is still a *N.meningitidis* antigen. A particulate antigen from at least one infective agent means that the agent is from the pathogenic organism regardless if it is produced from a non-pathogenic organism.

Claim 14 is vague and indefinite due to the phrase "characteristic of a micro-organism". It is unclear whether this statement is intended to imply. It is suggested that the claims be amended to "from a micro-organism" in order to eliminate ambiguity. This will not change the scope of the claim. With respect to "characteristic of a microorganism", whether or not a non-pathogenic microorganism is used to express an immunogen from a pathogenic microorganism, said immunogen is still from a pathogenic microorganism.

Claims 18 and 20 are vague and indefinite because it is unclear what is meant by a " 'common' mucosal immune response". They also refer to page 2, lines 15-29, of the specification. However, this passage and Example 6 do not use the term "common' mucosal immune response. Applicants can be their own lexicographer; however, they cannot add limitations which are not recited in the specification. Appropriate correction is requested.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 10 and 12-26 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tamura et al. (US 5,182,109).

Tamura et al disclose a vaccine preparation comprising in combination a vaccine and a bacterial toxin adjuvant. It is specifically disclosed that the toxin can be a B subunit of *E.coli* heat-labile enterotoxin or part of said B subunit or the B subunit of *Cholera* toxin, i.e., completely free of A subunit or toxic LT or CT holotoxin or both B subunits. It is further taught that the vaccine contained in the vaccine preparation can be influenza vaccine. Tamura also teach that any number of different vaccines can be used along with the *E.coli* B-subunit toxin or any of the other toxins, including CTB. Included in the list of vaccines to be used with one of the toxins are influenzae, Japanese encephalitis vaccine, mixed vaccine of pertussis, mycoplasma

vaccine, combined vaccine of measles, rubella and mumps, etc. See Column 8, line 60-column 9, line 65. It is taught that the Japanese encephalitis vaccines contains virus particles (Col. 8, lines 17-21). Example 19 teaches a mixed vaccine of measles, rubella and mumps with the LTB subunit. These vaccines comprise an association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms. Tamura teach that the vaccine can be intranasal vaccine or can be in injectable form, spray form or oral administration form. CTB alone (without CT holotoxin) and LTB alone (without LT) were still shown to be effective adjuvants and, unlike CT or LT, present no problems upon intranasal administration (see column 8, lines 56-57). The instant claims do not differ structurally from those taught by Tamura. Methods for the induction of a mucosal immune response as well as a systemic immunoglobulin response are also taught.

Response to Applicant's arguments:

Applicants argue that Tamura fail to disclose at least one particulate antigen. This has been fully and carefully considered but is not deemed persuasive. The term "particulate" has been defined by the specification at page 4, lines 19-23, as any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms. Tamura also teach that any number of different vaccines can be used along with the *E.coli* B-subunit toxin or any of the other toxins. Included in the list of vaccines to be used with one of the toxins are Japanese encephalitis vaccine, mixed vaccine of pertussis, mycoplasma vaccine, combined vaccine of measles, rubella and mumps, etc. Example 19 teaches a mixed vaccine of measles, rubella and mumps with the LTB subunit. This mixed vaccine clearly contains "an association of bacterial

antigens characteristic of the respective micro-organisms". It is taught that the Japanese encephalitis vaccines contains virus particles (Col. 8, lines 17-21). This vaccine also comprises an association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms. These are not single antigen vaccines, but are complexes of various antigens. Tamura teaches that their LTB subunit was free of A subunit. With respect to the claims referring to at least one influenzae antigen, the instant claims provide no structure for this antigen. The teachings of Tamura et al teach that *any* influenzae vaccine can be used in their methods and are not limited to the vaccine which was used in the Examples. Accordingly, the aggregated vaccines taught in the prior art which include more than one antigen are included in the scope of Tamura's invention.

Applicants argue that Tamura does not describe Cholera B subunits free of A subunits. This argument is not commensurate in scope with the claimed invention set forth in claims 10, 12-21 and 27 which are drawn to LTB not CTB. Cholera toxin subunit B is not included in those claims. With respect to claims 22-26, Tamura does several comparisons of the isolated CTB and the CT holotoxin. It is disclosed that CT is more effective than CTB as an adjuvant; however, it is highly toxic with known side effects. CTB alone, without CT holotoxin, is still shown to be an effective adjuvant and, unlike CT, presents no problem upon intranasal administration (see column 8, lines 56-57). The instant claims do not differ structurally from those taught by Tamura. Tamura specifically teach that CTB alone, without holotoxin, was found to be an effective adjuvant. The fact that other journal articles by the inventor Tamura mention

the use of holotoxin when using recombinant LTB does not effect the instant rejection which teaches that CTB/LTB subunits effectively acted as adjuvants with their mixed vaccines, single immmunogens, or associated particles and did not require the use of holotoxin. The compositions taught in the Tamura patent do not structurally differ from the compositions recited in the instant claims. Accordingly, the compositions taught by Tamura would inherently possess any of the properties of Applicants' claimed compositions, including the ability to provide an adjuvant effect without the use of holotoxin. With respect to the 2002-2003 catalog which teaches a 95% pure CTB, the CTB used by Tamura was prepared in 1989 or earlier. It is unclear that these are the same products. Further, the methods taught by Tamura et al do not require the use of Sigma purchased CTB. Any CTB free of the A subunit is encompassed by the teachings of Tamura. As stated above, claims 12-21 and 27 use LTB not CTB so the argument is moot with respect to these claims. Additionally, it is noted that the prior art at the time the invention was made was replete with references to both the CTB and LTB subunits' ability to act as adjuvants minus the A subunit. Further, the prior art at the time the invention was made taught how to obtain these subunits recombinantly. The Tamura patent states that the B subunits were free of the full-length toxin and active A portions.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 10-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura (US 5,182,109) in view of any one of Hirst et al (WO 90/06366), Kikuta et al or Hirabayashi et al. or Fujisawa et al (US 5241053).

The teachings of Tamura et al are set forth above. However, they do not particularly exemplify the use of a recombinantly produced CTB or LTB subunit in their methods.

Hirst et al disclose heat-labile toxin B subunit fusion proteins. The fusion proteins are prepared by recombinant DNA methodology. The LTB gene was well known. Page 5, lines 10-17, disclose a means for recombinantly producing the LTB subunit. It is disclosed that fusion proteins in which an antigen or epitope is fused to the carboxy-end of LTB represents a way of effectively presenting the antigen or epitope to the immune system. LTB is the carrier for the antigen/epitope. It is disclosed that any amino acid sequence having biological activity may be fused to the carboxy-terminus of the LTB. The antigen or epitope may be derived from a virus, bacterium, fungus, yeast or parasite. More specifically, the antigen may be derived from influenza virus, see page 3, line 23. It is also taught that attenuated live vaccines capable of expressing the fusion protein or killed toxigenic strains of E.coli in which the fusion protein has been expressed may also be used as vaccines. The vaccine may be administered orally, parenterally, or by any convenient means.

Kikuta and Hirabayashi both teach vaccine compositions comprising influenza HA antigens and cholera toxin subunit B. The vaccines induced both high levels of antiviral nasal IgA and serum HI antibodies, as well as complete protection against the homotypic virus infection. The vaccine composition of either Kikuta et al or Hirabayashi et al are identical to the claimed vaccine compositions. It is specifically disclosed that the B subunit of cholera toxin (CTB) used in their experiments was purchased from Sigma Chemical and did not reveal any detectable contamination with A subunit as determined by SDS-PAGE. Additionally, pyrogen activities which could be accounted for by contaminating substances such as lipopolysaccharide were not detected in the CTB preparation. See top of page 244, column 1, from Hirabayashi and top of page 596, column 1, from Kikuta et al.

Fujisawa et al teach fusion protein compositions produced and expressed recombinantly, comprising the gene encoding LTB and glycoprotein D from herpes simplex virus. The reference teaches that the fusion proteins may be formulated into vaccine compositions and administered to animals (col. 1-6, 7-12, abstract and claims). The fusion protein compositions and methods of the prior art are the same as the claimed vaccine compositions and methods.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that any purified CTB or LTB, whether prepared recombinantly, synthetically or isolated naturally could be used in the methods and compositions taught by Tamura et al. Tamura teaches the use of free CTB or LTB which are completely free of the A subunit and holotoxin in their compositions which include particulate immunogens, i.e.,

combined vaccines, Japanese encephalitis vaccine comprise particulate viral antigens, etc.. As the secondary references demonstrate, it was long known in the prior art that the LTB and CTB subunits were effective adjuvants whether used in fusion proteins or in mixed compositions. The secondary references teach the nucleotide sequences for the B subunits and teaches how to make these subunits recombinantly. This recombinant production of B subunit would not contain any other antigens, such as holotoxin, and would be highly purified. Recombinant technology has been long used for the overexpression of desired antigens and ensures purity of the antigen. It would have been prima facie obvious to one of ordinary skill in the art to produce the LTB or CTB subunit recombinantly and use it along with the particulate immunogens taught by Tamura et al. to enhance the immune response to these antigens. The teachings of Tamura et al only require the use of CTB or LTB free of the holotoxin and A subunits and do not require how theses subunits are made or where they are purchased from. Accordingly, it would have been obvious that recombinantly produced B subunits or subunits purchased from companies other than Sigma could be used in their methods. As stated above, Tamura et al teaches using these B subunits with large particulate or aggregated immunogens and does not limit their use to solely single peptide antigens. Tamura et al teach the use of any influenzae vaccine in their methods and are not limited to the particular one used in their examples, i.e., vaccines comprise both HA and neuraminidase which were well known in the art at the time the invention was made are included in the teachings of the Patent. Those of ordinary skill in the art would have a reasonable

expectation that the B subunits would work as an adjuvant whether a single antigen or an associated antigen were used.

Status of Claims:

8. No claims are allowed. The prior art teaches that CTB and LTB, free of A subunits or holotoxin, are effective adjuvants to single peptides, antigens, whole cell vaccines, associated viral particles, etc..

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jennifer Graser
Primary Examiner
Art Unit 1645

11/5/03